BRCA is not the only cancer gene .... and other controversies in cancer genetic counseling and testing

Guest Expert:
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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This week Francine and Lynn welcome Dr. Ellen Matloff. Dr. Matloff is director of the Yale Cancer Genetic Counseling Program and Research Scientist in the Department of Genetics. Here is Dr. Francine Foss.

Foss Let’s start off by having you tell us what a genetic mutation is?

Matloff A genetic mutation is a change in a gene that makes it impossible for the body to read the gene the way it should be and so it interrupts the function of the gene and in my area of cancer genetics, if a person carries a mutation it often means that they are at greater risks of developing certain types of cancers.

Foss Can you briefly tell us how you actually find out that a patient has a mutation? What are the tests that are done to find that out?

Matloff A genetic test is a test generally done on a blood sample. It can sometimes also be done on a saliva sample or even a scraping from the inside of the mouth/cheek and it is a test that can test for variety of different cancer genes. There are now dozens of different cancer genes available for testing.

Wilson Ellen, tell our listeners what a gene is and how it works, do we have a lot of them?

Matloff I think the best way to think about genes is that genes are the blue print for our body, and so on every single cell of our bodies, we have a blue print that tells us how tall we are going to be, our eye color, our hair color, are we at increased for diabetes, are we at increased risk for certain types of cancers and that blue print really guides a lot of our development and it is same blue print present in every single cell of our body, and we now know that we have about 20,000-30,000 genes for different traits, some of them diseased traits and some of them mundane traits, like how much ear wax you are going to make or what your eye color will be, or will you have wavy hair.

Foss It seems pretty amazing that we can do this type of genetic testing and look at all these different genes. How expensive is this and how long does it take to actually do the test?

Matloff Well, there are a lot of different tests, so the cost of the test and how long it takes really depends on which test you are ordering, and what I tell you tonight is going to be very different from what I would tell you even 2 years from now, because the way we currently do this is that we basically

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cherry pick for each person which genes need to be tested. So the test I usually order for cancer genes cost somewhere in the range of $3000-$4000 for most patients, but new technology available now and coming to the marketplace for less than $2000 will allow people to test their whole genome, so all of the genes in the genome will be tested from this one sample for less money than it costs me now to order just a couple of genes, so things will change very quickly.

Wilson We have heard about BRCA1 and BRCA2 for breast cancer, but what are some of the other genetic mutations that can be associated with breast cancer?

Matloff I am glad you asked because often times people think there is one breast cancer test and it is for BRCA1 and BRCA2 and if you have that you have had everything and in fact, breast cancer can be associated with a lot of different mutations that can be part of a different syndrome that includes breast cancer and thyroid cancer and a syndrome called Cowden disease caused by mutations and a gene called PTEN. It can be a part of a syndrome that causes many different types of cancers including cancers of the adrenal gland and lung, lymphoma, leukemia, childhood cancers and those are mutation in the gene called P53. There are some genes like CHEK2 which cause an increased risk for breast cancer that really no one has heard of and gets no press no media and so really it’s not that there is one test for breast cancer genetics, there are many different genes involved.

Foss Is the same thing true for say ovarian cancer?

Matloff It is true for ovarian cancer and so a lot of people again associate ovarian cancer with BRCA1 and 2, and we have recently had several cases that are tragic where very well meaning physicians have ordered genetic testing for their patients with ovarian cancer and they have ordered BRCA1 and BRCA2 and when it comes back negative the patient has been told, this is not hereditary in your family, and then we see other family members go on to develop and die from either ovarian, uterine, and/or colon cancer which are all cancers in the part of the spectrum from that syndrome which is called Lynch syndrome.

Foss It is sounds like you are pointing out that it is crucial if a patient is going to have genetic testing that they have the right kind of genetic testing.

Matloff Absolutely, and I can remember when we started this testing in about 1996, our greatest fear was insurance discrimination and we thought, a lot of people have this, they are never going to get health insurance, they are going to be doomed, and that was our greatest fear, and really that has not played out, health insurance has not been the greatest risk. It is the risk that the wrong test will be ordered and that the result will be misinterpreted, that’s what we are seeing as the major fall out from genetic testing.

Wilson As I said, we have all heard of this BRCA testing. Why is that something that everyone seems to have heard of, but many of these other important tests have been flying below the radar. Why is that?

Matloff BRCA1 and BRCA2 have received a lot of attention for lots of reasons. They were really the first genes discovered for a relatively common disease like breast cancer as opposed to a rare genetic disease that occurs in children like cystic fibrosis or muscular dystrophy that most people do not worry about, but a lot of people worry about breast cancer and then what happened is the United States Government issued a patent for BRCA1 and BRCA2 meaning that only one company in the world was allowed to do this testing, and so you can imagine this has created quite a monopoly for this company, and they even invested a lot of money in publicity, and so there have even been ads on television directly to the patients, ads in magazines directly to patients, and they heavily market it to physicians and health care providers to offer this testing, and that is probably why you have heard of it.

Wilson And does this tie into some of these kits that are available to physicians right in their office, so that they can do the test with the patient themselves so they do not even really need to deal with any outside entities? And then they would also be the same people to do any interpretation, is that correct?

Matloff You have got it, and so it is a nice neat little kit about the size of a Kleenex box and now they have even designed it so that you can just spit in the tube, it does not even require a blood sample and I saw a patient recently in her 70s’ whose family history was absolutely not consistent with the BRCA1 or BRCA2 mutation but she had had breast cancer in her 70s’ and was concerned, and so her doctor just handed her the kit and said if you want the test you fill out all the paper work and spit in this tube and send it in. These are the kinds of things that are happening.

Foss Is there a cost to the patient for this kit or is it covered by insurance?

Matloff The kit itself is free. It is just a cardboard box with some forms in it and a little vial either for blood or spit. But when you send the kit in, the test costs about $3400.

Foss And is that something that is covered by the patients insurance?

Matloff It depends, if the patient is a good candidate for testing, then they will likely meet their insurance companies criteria for testing. If they are not a good candidate for testing, then most often they will not be covered.
So in most situations if a patient does one of those kits, what is the follow up with the patient once the results come back, what happens next?

Well, if the kit has been sent out not from a genetic counseling office, I do not really know what happens. I have heard stories of patients on their cell phones driving in a car and get a phone call saying, by the way you carry the breast cancer gene. Not really great stories. What really should happen, and what the medical model outlines, is the thing that this is how it should be done is that the patient should come in before having testing, they should get genetic counseling so that we can take a 5 generation pedigree and determine first of all, does this look hereditary? Secondly, if it does look hereditary which gene is most likely mutated, is it BRCA1 or BRCA2, is it CHEK2, is PTEN, P53, is it something else? And then we can order the test, do preauthorization so that we can most likely get their insurance to cover, and then we meet with them again to give them their results in person to tell them not only what it is going to mean for them but what is going to mean for their children, their siblings, their parents, their aunts, uncles and cousins, because really this has an impact on the entire family, sons and daughters.

If I am interested in getting tested, or one of my family members is, and my or their physician is not familiar with this kit, there is advertising that you have mentioned, so can I go to an internet site and sign up for something and do it myself and send something in? Is that possible? And if so, that sounds like it is fraught with many of the same problems that you have just reviewed even related to the individual doctor's office that might do the test, but may not have the expertise in genetic counseling that you have.

There are now internet sites that you can go to and order not only some of the genes involved in cancer, but also some genetic changes that may or may not have anything to do with the predisposition of cancer, it is really a guess, and you can go to these sites and order these kits and it is kind of interesting because you get back this huge report that tells you everything from, your ear lobes are likely attached or likely detached, what your likely eye color and hair color are, what your ancestry likely is, so some things that they call entertainment, and then rolled into it is they estimate your risk for breast cancer, prostate cancer, things like Lou Gehrig's disease, Parkinson’s disease, your risk for alcohol addiction, all of these very serious things and there are a couple of problems with it. First of all, many of them are faulty. The FDA did a major study of these companies and they did something that I thought was so brilliant, they took 5 DNA samples from 5 real people and sent them to different companies and then they sent the same 5 samples from those same 5 people but they changed their family histories, and sent them to the same companies, and what they got back was 10 completely different reports, and so different companies were testing for different snips or genetic changes and estimating different risks and the companies were also changing the genetic profile based on what the person wrote down as their personal or family
history which if you are looking at genetic changes should have no variation in what your DNA shows, and so the chance that you are going to get a fraudulent result is unfortunately high.

Foss

Ellen, this is all very confusing as to how this is actually regulated, or is it regulated, at the level of the FDA and federal government?

Matloff

In terms of the direct to consumer testing available on the internet, it really is not regulated well and there have been several calls to the FDA to step up regulation but the problem is the FDA is understaffed and under worked even when it comes to things like medications, and so for them to get involved in something like direct to consumer genetic testing is difficult and so far we have very little regulation.

Foss

And the kind of genetic testing that a patient would have say if they came to Smilow Cancer Hospital, is very different than the level of testing that you get from an internet test site?

Matloff

It is quite different and we test for genes that have been validated. They are in labs which are clear and approved, so those are laboratories that are clinically approved to give the highest level of results for patients and also you have someone ordering and interpreting the test who actually knows what they are doing which is important.

Wilson

It sounds like that is really a key piece of his puzzle. It is very different for someone sending in their own DNA to get evaluated and then opening up an envelope with a piece of paper explaining things to them then at Smilow where they would meet with you or one of your staff prior to testing and after the testing, and you would be having a conversation with them about what all this really means.

Matloff

Absolutely and obviously I am biased. I am the Director of Cancer Genetic Counseling here and I really do think that is the order in which things should happen, but we have now had the chance over the last few years to see the fall-out of what happens when things are not done in that order, and we have seen family members develop cancer and die. We have even seen patients who had well meaning physicians who just read the results wrong and interpreted a true mutation as a normal test result and so the patient did not do the things they needed to do knowing they are at high risk just because their test result was completely misinterpreted.

Wilson

We are going to take a short break for a medical minute. Please stay tuned to learn more information about genetic mutations with Ellen Matloff.

15:15 into mp3 file http://yalecancercenter.org/podcasts/2011_1113_YCC_Answers_-_Ellen_Matloff.mp3
Medical Minute There are over 12 million cancer survivors in the United States right now and the numbers keep growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. The return to normal activities and relationships may be difficult and cancer survivors face other long term side effects of cancer including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers such as one at Yale Cancer Center, to keep cancer survivors well and focused on healthy living. This has been a medical minute, brought to you as a public service by the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and my co-host is Dr. Francine Foss. Today we are joined by Ellen Matloff and we are discussing genetic mutations. Ellen, we talked a lot about the facts and some of the controversies in the first part of the show. What’s going on with the future regulatory status? Francine had brought up the FDAs regulatory abilities over these things, and it sounds like it is pretty controversial. How serious is this in terms of the government getting involved? Are these patterns being upheld?

Matloff This is extremely controversial and when you think of the history of BRCA1 and BRCA2 think of it this way, there were 100s of researchers from around the world, many funded by the NIH, the National Institute of Health, with our tax dollars. So basically, we were paying for this research and the search for BRCA1 and BRCA2 and researchers were sharing information nationally and internationally to find these breast cancer genes, and then after this huge collaboration one researcher applied for patents and was somehow issued these patents on BRCA 1 and BRCA2, shutting down testing everywhere else, and so imagine what would happen if this continued and every time an important gene was found someone patented that gene and enforced the patent in such a way that no one else can study it, no one else can test for it, and no one else can look at it. Instead of having whole genome sequencing available, even one company is now offering it for $1000 without interpretations, we could be looking at genetic testing costing $100,000 and why should your listeners care about this? Well, many-many issues effect only a small segment of the population, but when you think about the DNA, DNA effects men and women, people of every ethnic background around the globe, people of every age, people with every health history background, every disease history background, men, women, children, people who are 95 years old, everyone has DNA, and we have the ability with our knowledge from the human genome project to use this information to predict disease, and to make health care more effective and more efficient. It would be less expensive to manage people. If we can use this information for the greater good, these companies, if they have these patents and enforce them and create monopolies to make millions and millions of dollars, it is going to halt that so we should all care about this.

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Wilson: So that we fully understand this, to patent the ability to test for certain genetic mutations or genomic makeup seems very different than me, in a laboratory, discovering a new molecular pathway for which I develop a new drug to treat cancer and block that cancer pathway, and have a company that makes that drug because I made that discovery, but that just applies to that one discovery, that drug, that one mechanism, so is that really what the difference is here is in terms of patent protections?

Matloff: Absolutely, I mean if someone develops a new drug, or a new radiation therapy machine or a new surgical instrument or technique or device, they are creating something new. These genes were not created by the people holding the patent that is very-very clear, they created absolutely nothing new and yet they have a patent on these genes.

Foss: Ellen, is this being challenged in court?

Matloff: It is, and let me disclose that I am a plaintiff in the lawsuit against this company and the lawsuit is being sponsored by the ACLU and it is a handful of clinicians in several major organizations against Myriad Genetics in Salt Lake City, Utah, and we are now asking The Supreme Court to take this case, and we are very-very hopeful that they will. They only take a few cases a year, but as I mentioned DNA is a universal issue, something that affects everyone and if we do not take a stand on this now, it is going to halt medical care in terms of genetics as we move forward.

Foss: There are other new and rare genes that are being discovered that are associated with human diseases, are these currently going down the same path?

Matloff: There are hundreds and hundreds of patents on genes, but only a minority of those patents have been upheld, restricted and monopolized the way that BRCA1 and BRCA2 have. Many researchers have patents and they have a small licensing fee, they resolved it in other ways, nothing like we have seen in BRCA1 and BRCA2, and so what this company may have done, they may forever change the patent system for everyone doing genetic research.

Wilson: Recently, I understand your program expanded.

Matloff: Yes.

Wilson: Tell us about that expansion and what other plans you have for the future, is the first part of the question, the second part of the question is, how does someone get in touch with your program, what is involved for a patient to get access to your expertise and your team?

Matloff: We are expanding and we are expanding for several reasons. We are expanding because we are
creating outreach clinics to hospitals in Connecticut. We recently started one at Griffin Hospital, in Derby, Connecticut at their very beautiful facility there. We have a long standing outreach clinic at Greenwich Hospital, and we have had that partnership with them for more than a decade, and there are several other hospitals who are now interested and we are in contract negotiation, but one of the other reasons we are expanding is that we are part of a very exciting initiative with Elena Ratner from gynecologic oncology and Erin Hofstatter from breast oncology here at Smilow, and so the three of us, genetics, gynecologic oncology and breast oncology are teaming up for the first time for a clinic called the Take Charge Clinic, and I like the name of the clinic because it is really about learning your risks and taking charge of your risks and learning what you can do to reduce those risks. We are beginning with patients who are at high risk for breast and/or ovarian cancer, and they are going to come to me for risk assessment and for genetic testing, and then if we learn that they are at high risk for breast and/or ovarian cancer, they will see the other members of the team, not only to address the breast and ovarian cancer risks, but also to address the many lifestyle changes and side effects, all the things that can occur, for example, if a young premenopausal woman has to have her ovaries and fallopian tubes removed because she is at such a high risk for ovarian cancer. Unfortunately, some of those things have fallen by the wayside up until now because people are just too anxious to get those ovaries and fallopian tubes out, and they are happy if the pathology comes back and no cancer is found, but what about a 38-year-old woman who goes into surgical menopause overnight, and now, hopefully, has 50 more years to live? How we dealing with the side effects of that? The impact on heart disease, bone health, sexuality, body image, the relationships in her life? Those are some of the things that we are going to deal with within the Take Charge Clinic.

Foss

Can you identify for our listeners how a woman would know that they are at high risk for one of those two diseases?

Matloff

There are many things that make people aware that they are at increased risk, one of them is family history, if you have a family history of breast cancer, particularly a breast cancer that is diagnosed before the age of 50 and is found in multiple family members within the same bloodline, and you have a family history of ovarian cancer or fallopian tube cancer or primary peritoneal cancer, we know that that group of people are definitely at a higher risk. If there is a family history of male breast cancer, of a triple negative breast cancer or a breast cancer that when that tumor is sent to pathology it is tested estrogen receptor, progesterone receptor and HER2-negative, if you are of Jewish ancestry and you have a family history of breast or ovarian cancer, these are all little things that should make you think that you may be at increased risk. There are also personal findings, so for example, if the person them self has had breast or ovarian cancer, particularly at a young age, or for a person who has had a breast biopsy that showed atypical hyperplasia or lobular carcinoma in situ, all of those things could put them at increased risk for breast and/or ovarian cancer.
Foss: Ellen, do you have a website or a contact if women are interested in this particular clinic?

Matloff: The clinic is underdevelopment, but if people are interested they can call our general line, which is 203-764-8400. They can also look at our website by googling Yale Cancer Genetic Counseling and it will bring you right to our website.

Wilson: And does your team see patients who do not have perhaps a significant family history of cancer, but are just worried about these things, because they have read about it, they have seen it on TV and they are concerned about what their genes may harbor and are interested in getting access to an expert like yourself or one of your team members as opposed to sending in saliva, that type of thing? Can someone who may not be at high risk seek your services?

Matloff: Believe it not, we have seen people who have a friend who died of breast or ovarian cancer and they just have heightened concern, and they want to come and learn about their risks and learn their options, so yes, we can see people like that and one of the great things about the Take Charge Clinic is now anyone who thinks they are at risk can be funneled into the genetic counseling and risk assessment funnel, we are calling it, and we can determine by a formal risk assessment if they really are at risk and need other services or if their risks are really that of someone in the general population and they do not need a costly breast MRI, they do not need to take a medication like tamoxifen, which also has side effects like all medications do. So, we are trying to use this to give them a true feeling of risk with real data.

Foss: Ellen, there are also a lot of patients that you see I am sure that have these genetic mutations that may or may not end up developing cancers, so what percentage of patients with the genetic mutations actually go on to develop a cancer?

Matloff: This is a great question, and again it is very mutation dependent, so with genes like BRCA 1 or 2, the chance of developing breast cancer is between 55% and 85% for a female carrier as compared to the general population risk of breast cancer at about 12% to 13%, so that is markedly increased. With the mutation in a gene like CHEK2, there may be increased risk of breast cancer, but it is not quite that high and with the mutation like P53, the risk of a whole series of cancers may be even higher than we see with BRCA1 and BRCA2.

Foss: Could you close by telling us what you think the future is in genetic testing?

Matloff: I will tell you what I hope the future is in genetic testing. I hope that in the very near future genetic patterns will no longer hinder clinical testing and care, and that we will be able to offer this whole exome sequencing to patients at a very reasonable cost, so that in the future, instead of saying that every woman should have a mammogram at 40, we can say, based on your genetic

profile you should have one at 25 and who knows, maybe someone else should have one at 50, and this would be with every type of cancer and many-many diseases, that is the hope for the future.

*Dr. Ellen Matloff is the director of Yale Cancer Genetic counseling program and research scientist in the department of genetics. If you have questions you would like to add your comments, visit [yalecancercenter.org](http://yalecancercenter.org), where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.*